Androgen insensitivity syndrome

Numerous clinical syndromes are now recognised to be associated with resistance to the action of hormones in target tissues. There is no clearer clinical example of this phenomenon than the development of an external female phenotype in a genetic male, in whom there is total resistance to the action of androgens, the so-called androgen insensitivity syndrome. Approximately two thirds of cases of androgen insensitivity are familial with an X linked pattern of inheritance.

Clinical phenotypes

Two phenotypic forms of the androgen insensitivity syndrome are recognised. The complete form (CAIS), previously known as the testicular feminisation syndrome, is associated with normal female external genitalia. The condition may present in infancy or childhood with labial swellings or inguinal hernias that are found to contain testes. More typically, CAIS presents in late adolescence with primary amenorrhoea. There is absence of female internal genitalia on ultrasound scan or laparoscopy and testicular histology shows spermatogenesis to be incomplete or absent, although Leydig cells are abundant. Plasma testosterone concentrations are within the age appropriate male range or in some instances even higher as a result of the increased stimulation by luteinising hormone. The partial form of the androgen insensitivity syndrome (PAIS) is associated with a wide range of genital abnormalities, and typically presents at birth with genital ambiguity. Severe hypospadias and associated abnormalities such as a microepispadias, bifid scrotum, and bilateral cryptorchidism are common. Additionally, the external genital phenotype may be predominantly female with partial labial fusion and clitoromegaly. Clinically milder forms of PAIS may also include isolated familial hypospadias and some cases of infertility in otherwise phenotypically normal males. The diagnosis of PAIS depends on demonstrating a normal testosterone response to human chorionic gonadotrophin (HCG) stimulation. Measurement of steroid precursors in plasma and their metabolites in urine after HCG stimulation should exclude other testosterone biosynthetic defects. Pelvic ultrasound generally shows absence of female internal genitalia, although vaginal remnants may persist. As male pseudohermaphroditism due to a number of different causes may present with a clinical phenotype similar to PAIS, careful evaluation is clearly important to optimise management.

Investigation

The following approach is suggested for the investigation of patients with male pseudohermaphroditism. Examination of the internal genitalia by ultrasound scan or by laparoscopy is needed to look for evidence of Mullerian structures such as a uterus. An opportunity should be taken at the time of any reconstructive surgery to examine, if possible, gonadal histology in case of dysplasia or true hermaphroditism. An HCG stimulation test (1500 units daily for three days) with normal testosterone production is a prerequisite if a diagnosis of PAIS is to be considered. Testosterone biosynthetic defects can be excluded by measurement of steroid precursors such as 17 hydroxyprogesterone, androstenedione, dehydroepiandrosterone and its sulphate. The autosomal recessive disorder, 5α-reductase deficiency, can be excluded by measurement of testosterone and dihydrotestosterone in plasma together with 5α- and 5β-reduced androgen metabolites in urine after HCG stimulation. Further information about possible androgen insensitivity can be obtained from androgen binding studies and molecular analysis of the androgen receptor gene.

Androgen binding studies

The evidence that androgen insensitivity occurs because of some abnormality in the androgen receptor was first obtained...
from assays of androgen binding activity in genital skin fibroblasts. A range of androgen binding abnormalities have been defined, but a general classification describes binding as negative, deficient, or positive. The majority of patients with CAIS have negative or deficient binding, whereas PAIS is usually associated with positive binding. Qualitative defects in androgen binding are found in approximately 10% of patients with PAIS.

Management of PAIS is more complicated. The critical problem is the current lack of a reliable indicator of whether an infant reared as male will virilise at puberty. Trying to establish a precise diagnosis is clearly important, but often takes a considerable time. The paediatric surgeon must be involved at an early stage when assessing the anatomy of the external genitalia. Occasionally, a trial of androgen treatment will be helpful, for example, a course of monthly injections of testosterone enanthate (25 mg) for two to three months may be required, before finally deciding whether a severely undervirilised infant can be reared as a male. It is important to delay birth registration until a decision has been made. Although the term PAIS implies that virilisation will not occur in the long term, this may not be the case, even when there is a mutation of the androgen receptor gene. PAIS patients reared as females require appropriate genital surgery and gonadectomy performed early and oestrogen replacement at the time of puberty. In PAIS males, repairing a severe hypospadias and bringing the testes down into a normal scrotum is a task most surgeons choose to perform at about 3 years of age. Preoperative androgen treatment may produce phallic growth and facilitate surgical reconstruction.

The androgen insensitivity syndrome is currently one of the subjects of study undertaken through the auspices of the British Paediatric Surveillance Unit. The survey should provide details on precise diagnosis as well as some indication of the incidence and prevalence of the condition. It is only when such information becomes available that it is possible that recent knowledge of the molecular biology of androgen action may be used to predict the longer term outcome of androgen insensitive patients reared as males.

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